REGULATION OF ALCOHOL INTAKE BY ANGIOTENSIN MECHANISMS, L. A. Grupp and S. Harding, Biobehavioral Research Department, Addiction Research Foundation of Ontario and Department of Pharmacology, University of Toronto

Angiotensin (ANG) II is an octapeptide present in the circulation, but also locally produced in peripheral tissue and in brain. ANG II causes a dose-dependent, antagonist reversible suppression of voluntary alcohol drinking mediated by the AT_1 receptor subtype. The inhibitory effect is specific to alcohol since water intake is enhanced and glucose intake is unaffected by this peptide. Since ANG II does not alter the absorption, distribution or metabolism of alcohol, its effect is not the result of a change in drug handling. Subfornical organ lesions attenuate the inhibitory effect, yet infusions of ANG II into the third or fourth ventricles enhance water intake but do not suppress alcohol consumption. These findings suggest a specificity in the brain circuits that mediate ANG II's effect and dissociate its effects on water intake from its effects on alcohol intake.

Many manipulations which reduce alcohol consumption are correlated with changes in ANG II activity. For example, the beta adrenergic agonist, isoproterenol, or the serotonin uptake inhibitor, fluoxetine, stimulate ANG II and reduce alcohol drinking. Low salt diets activate while salt-supplemented diets suppress ANG II activity and are correlated with enhanced or reduced alcohol consumption respectively. Genetically selected animal lines such as the NP rats or DBA mice which avoid alcohol show elevated ANG II levels compared to their high alcohol drinking P and C57/B1 counterparts which have lower levels of ANG II activity. Finally, hypertension is associated with chronic alcohol consumption and studies have shown that high ANG II hypertension is associated with low alcohol consumption while low ANG II hypertension is associated with high alcohol consumption.

These actions of ANG II suggest that it may represent a satiety signal and recent experiments indicate that it might produce satiety by engaging glucoregulatory mechanisms. In one study, injections of tolbutamide, a drug which releases insulin and blocks glycogenolysis, reduced alcohol intake when administered alone, yet when combined with ANG II, attenuated its suppressive effect on alcohol intake. In a second study, isoproterenol, an adrenergic agonist which stimulates glycogenolysis, also reduced alcohol intake. This effect was attenuated by indomethacin, a drug which is known to decrease glycogenolysis. In a final study, glucose injections attenuated morphine's ability to stimulate alcohol intake. Taken together these findings suggest that a satiety function mediated by glucoregulatory processes may be a broad explanatory concept for the inhibitory effect of ANG II and isoproterenol on alcohol intake and may be general enough to explain the suppressive effects of other peptides and transmitters on alcohol consumption.